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10/733,617	12/11/2003	Ming-qun Xu	NEB-214-US	9524
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HARRIET M. STRIMPEL; NEW ENGLAND BIOLABS, INC. 240 COUNTY ROAD IPSWICH, MA 01938-2723			EXAMINER VENCİ, DAVID J	
			ART UNIT	PAPER NUMBER
			1641	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/733,617

Applicant(s)

XU ET AL.

Examiner

David J. Venci

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on March 26, 2007.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) 9-31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-31 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 03/26/07.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

## DETAILED ACTION

Examiner acknowledges Applicants' reply, filed February 21, 2007, which amends claims 1, 4, 5 and 7. Claims 1-31 are pending in this Application. Claims 9-31 are drawn to non-elected inventions and were withdrawn from consideration in the Office Action dated February 28, 2005. Currently, claims 1-8 are under examination.

### *Specification*

The disclosure is objected to because of the following informalities:

On p. 30, paragraph beginning on line 9, third sentence, the phrase "reactive C-terminal thioester on one of the carrier or ligand is the product of intein cleavage in the presence of a thiol reagent" is indefinite in view of:

1. the general definition of "intein" recited on p. 20, lines 5-8. According to p. 20, lines 5-8, an "intein" is a "self-splicing protein". However, Examiner is unable to correspond a "self-splicing protein" to any object in the phrase "reactive C-terminal thioester on one of the carrier or ligand is the product of intein cleavage in the presence of a thiol reagent". Whether "a thiol reagent" effectuates "self-splicing" is not clear.
2. Figure 1. According to Fig. 1, an "N-S acyl shift" generates a C-terminal thioester (*i.e.*, the phrase "reactive C-terminal thioester on one of the carrier or ligand is the product of intein cleavage in the presence of a thiol reagent" appears mechanistically false in view of Fig. 1). Furthermore, according to Applicants' specification Fig. 1, "2-

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mercaptoethanesulfonic acid" cleaves said "carrier-intein fusion protein" to generate an N-terminal cysteine (*i.e.*, not the claimed "C-terminal thioester").

3. the prior art as evidenced by Assignee's publication, Cantor & Chong, 22 PROTEIN EXPR. PURIF. 135 (2001). According to Cantor & Chong, an "N-S acyl rearrangement" generates a thioester (see e.g., paragraph bridging pp. 135-136, sixth sentence, "the thiol ester bond formed by an N-S acyl rearrangement") and "2-mercaptoethanesulfonic acid" cleaves said "carrier-intein fusion protein" to generate an N-terminal cysteine (see Fig. 1, step 2). The phrase "reactive C-terminal thioester on one of the carrier or ligand is the product of intein cleavage in the presence of a thiol reagent" appears mechanistically false in view of Assignee's publication.

Appropriate correction is required.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1:

The terms "intein" and "carrier-intein fusion protein" are indefinite. According to Applicants' specification, an "intein" is a "self-splicing protein" (see Specification, p. 20, lines 5-8). However, Examiner is unable to correspond a "self-splicing protein" to any object in claim 1. Furthermore,

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Examiner is unable to discern any "self-splicing" step anywhere in claim 1. Whether "2-mercaptoethanesulfonic acid" effectuates "self-splicing" is not clear. Clarification is required.

The phrase "wherein a carrier-intein fusion protein is cleaved in the presence of 2-mercaptoethanesulfonic acid to generate the C-terminal thioester" is indefinite. According to Applicants' specification Fig. 1, an "N-S acyl shift" generates a C-terminal thioester (*i.e.*, the phrase "wherein a carrier-intein fusion protein is cleaved in the presence of 2-mercaptoethanesulfonic acid to generate the C-terminal thioester" appears mechanistically false in view of Fig. 1). Furthermore, according to Applicants' specification Fig. 1, "2-mercaptoethanesulfonic acid" cleaves said "carrier-intein fusion protein" to generate an N-terminal cysteine (*i.e.*, not the claimed "C-terminal thioester"). Clarification is required.

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***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Nock & Sydor (US 2002/0049152).

Nock & Sydor describe a method for purifying a ligand-binding molecule from a mixture, comprising:

(a) adding 2-mercaptoethanesulfonic acid (see *e.g.*, para. [0059], "2-mercaptoethanesulfonic acid") to a thioester (see *e.g.*, para. [0056], "The splicing reaction involves an acyl rearrangement between the S [of a cysteine] at the N-terminal of the intein with the peptide bond which connects [the cysteine] to the N-extein") (paraphrasing mine) attached to a carrier (see *e.g.*, Fig. 1B, "polypeptide"), thereby forming a carrier-ligand conjugate (see *e.g.*, para. [0059], "The activating compound then becomes attached to the end of the extein that was adjacent to the intein"; see *also*, Fig. 1B);

(b) non-covalently binding the carrier-ligand conjugate to a matrix (see *e.g.*, para. [0023], penultimate sentence, "this [carrier-ligand conjugate] is immobilized to a surface[...] through covalent and/or non-covalent interactions to form a [carrier-ligand conjugate] that is immobilized to a surface" (paraphrasing mine); see *also*, para. [0049], second sentence, "subsequently

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immobilized to a surface"), and contacting the carrier-ligand conjugate with a mixture containing the ligand-binding molecule to selectively bind the ligand-binding molecule to the carrier-ligand conjugate (see para. [0135]); and

(c) eluting the ligand-binding molecule from the ligand so as to obtain the purified ligand-binding molecule (see para. [0136]).<sup>1</sup>

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<sup>1</sup> With respect to the added functional language requiring elution "under conditions in which the carrier-ligand remains non-covalently bound to the matrix", Examiner observes that Nock & Sydor describe methods incorporating a "chitin binding domain" (see para. [0066]) for binding carrier-ligand conjugates to matrices (see para. [0065]). Nock & Sydor's description of a "chitin binding domain" appears identical to Applicants' disclosed non-covalent matrix—carrier-ligand conjugate combination (see Specification, paragraph bridging pp. 22-23). Absent objective evidence to the contrary, Examiner posits that Nock & Sydor's description of a "chitin binding domain" is functionally equivalent to whatever structural limitations may be required by said added function language in claim 1.

***Response to Arguments***

*Claim Rejections - 35 USC § 112*

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, because the terms "intein" and "carrier-intein fusion protein" are indefinite. According to Applicants' specification, an "intein" is a "self-splicing protein" (see Specification, p. 20, lines 5-8). However, Examiner is unable to correspond a "self-splicing protein" to any object in claim 1. Furthermore, Examiner is unable to discern any "self-splicing" step anywhere in amended claim 1. Whether "2-mercaptoethanesulfonic acid" effectuates "self-splicing" is not clear.

In response, Applicants point to the specification p. 30 for solution to the aforementioned claim deficiencies.

Herein, Examiner raises new objections to the specification p. 30.

*Claim Rejections - 35 USC § 102*

In prior Office Action, claims 1-8 were rejected under 35 U.S.C. 102(e) as being anticipated by Muir *et al.* (US 6,875,594).

In response, Applicants amend independent claim 1 to add, *inter alia*, a method requiring "2-mercaptoethanesulfonic acid".

Applicants' amendment is sufficient to overcome this rejection. Accordingly, this rejection is withdrawn.

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In prior Office Action, claims 1-8 were rejected under 35 U.S.C. 102(e) as being anticipated by Nock & Sydor (US 2002/0049152).



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Notwithstanding issues of claim indefiniteness, addressed *supra*, Examiner amends the instant rejection to more accurately reflect Applicants' amended claims 1-8. Reconsideration of the instant rejection in view of Applicants' amended claims is respectfully requested.

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**Conclusion**


No claims are allowable at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci  
Examiner  
Art Unit 1641

djv

  
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